

REMARKS

Reconsideration of this application is respectfully requested.

Applicants acknowledge the allowability of claims 28 and 29 if amended to include the limitations of the base claim, as indicated in the Office Action.

Amendment to Specification

The specification has been amended to include a listing of the priority information, as directed by the Examiner.

Amendments to the Claims

Claims 32-40 are canceled without prejudice or disclaimer. Claims 3, 7, 12 and 19 have been amended to be limited to taxanes, as described further below. Claims 41-49 are added to more particularly describe the way in which the anti-tumor drugs of the invention are labeled and identify particular compounds that may be used in the method of the invention. Support for new claim 41 is described more fully in conjunction with the discussion of the rejections under 35 U.S.C. § 103 that follows. Support for claims 42-49 can be found in original claims 1 and 20-27. Entry of these claims is respectfully requested.

With this amendment, Claims 1-31 and 41-49 are pending in the application with claims 25-27 and 30-31 being withdrawn by the Examiner.

Restriction Requirement

The present application and claims are drawn to radio-labeled anti-tumor drugs and their use for imaging, diagnostic and treatment purposes. In the restriction requirement, the Examiner limited examination of the claims to ^{11}C -paclitaxel. Applicants maintain that the restriction is

improper in that, if an allowable species claim drawn to the single drug is discovered, then the Examiner should be required to search the other generic claims setting forth other species of drugs. Applicants further submit that, even if the Examiner disagrees, prosecution should proceed with consideration of the taxanes as a genus of compounds as set forth in the specification. Paclitaxel and docetaxel, while different, are related as being a part of a genus having structural and functional similarities (see original claims 20-31 and compare, for example, claims 29 and 30). New method claims 42-49 are directed to a genus that is limited to labeled paclitaxel and/or docetaxel.

Applicants understand that the Examiner has restricted the application at this time and have canceled claims 32-40, which are drawn to classes of anti-tumor compounds other than the taxanes. Claims 3, 7, 12 and 19 have been amended to claim only taxanes, in accordance with the proposed genus. It is respectfully requested that the Examiner reinstate claims 25-27 and 30-31, at which time claim 1 can be amended to refer to only the taxanes as a class. New claims 41-49 are drawn to various methods using various compounds that are radiolabeled paclitaxel and docetaxel.

Rejections Under 35 U.S.C. § 103

In the August 21, 2003 Office Action, the Examiner rejects claims 1-24 under 35 U.S.C. 103(a) as being unpatentable over Pagé et al. (U.S. Patent No. 5,981,564) in view of Li et al. (U.S. Patent No. 6,441,025) and in further view of a publication by Schirbel. Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation either in the references themselves or within the

knowledge of a person of ordinary skill in the art to modify or combine the references. Second, there must be reasonable expectation of success. Third, the prior art references when combined must teach or suggest all claim limitations. The teaching or suggestion to make the combination must be found in the prior art not in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that the rejection set forth by the Examiner is untenable. First, there is no motivation in the references to combine them in such a way that a person of ordinary skill in the art would arrive at the claimed invention. Second, even if one were to combine the references, one would not arrive at the claimed invention. Third, combining the references would lead to no reasonable likelihood of success with respect to the presently claimed invention. Fourth, even if one were to combine the references, the disclosure would be non-enabling.

The ^{11}C -paclitaxel claimed and used in the present invention is distinct from the paclitaxel derivatives disclosed in both the Pagé and Li references. As repeatedly stated in the specification, the present invention utilizes radio-labeled anti-tumor drugs which, but for the presence of an isotope, are identical to the drug itself. (See new claim 41) That is, the radio-labeled compounds used in practicing the invention do not have additional groups attached to the anti-tumor drug that cause differences in physical properties, nor are atoms replaced by atoms of a different element. Rather, non-radio-labeled atoms (for example, ^{12}C), are replaced by radioisotopes (such as ^{11}C). The Examiner's attention is drawn to, for example, page 9, line 3-4 and page 10, lines 28-30. This distinction between the presently claimed invention and the prior art, such as the references applied by the Examiner, is pointed out throughout the present specification and is now explicitly set forth in new claims 41-49.

Pagé discloses paclitaxel derivatives having an increased solubility in water, as stated on page 5 of the Office Action. Pagé specifically states that paxlitaxel disclosed by Pagé is “a derivative modified at the 2' or seven position.” (column 2, lines 41-43) As is also pointed in Pagé, the paclitaxel derivatives are “derivatives made from glutarylpaclitaxel to which different amino acids or glucuronide were conjugated.” (Column 2, lines 46-47). Further, Pagé admits that these derivatives show “cytotoxic activity similar to paclitaxel alone” (column 2 lines 48-49), i.e. its properties differ from paclitexel. The present invention is not drawn to radiolabeled “derivatives made from glutarylpaclitaxel,” derivatives having an increased solubility in water, nor derivatives with “cytotoxic activity similar to paclitaxel alone.” The present invention is drawn to radio-labeled versions of the compound itself.

Applicants further note that on page 5 of the Office Action, the Examiner points out that the structures claimed by Pagé are set forth by formula 1 in columns 3 at lines 17-40. The Examiner states that this structure is paclitaxel if R and R' are both hydrogen. Although this is correct, at line 40, Pagé states that the claimed invention does not include compounds where both R and R' are hydrogen. Thus, Pagé specifically states that it is not concerned with paclitaxel itself, but with paclitexel derivatives.

Similarly, Li discloses water soluble compositions of paclitaxel formed by conjugating paclitaxel to a water soluble polymer. (See the Office Action, page 5, last paragraph). As stated in the Office Action, the compositions of Li are designed to “overcome the drawbacks associated with the insolubility of the drugs themselves.” Applicants note, however, that it is exactly these differences in properties between the approved anti-cancer drugs themselves and derivatives such as the conjugates of Li that the present invention seeks to overcome. (See for example, page 12, lines 120-20).

The Examiner states that Li discloses the use of labeled paclitaxel for imaging, referring to column 14, lines 19-30. However, a careful reading indicates that Li is not concerned with paclitaxel itself, but with derivatives and conjugates, as is clear from the specification. For example, at line 30, Li states that the use of the invention is for guiding the practitioner in the selection of patients to undergo chelator-paclitaxel therapy. Thus, unlike the present invention, Li is not concerned with paclitaxel itself, but rather with particular compositions in which paclitaxel is derivatized or associated with some other moiety such as a chelator or a conjugate.

The Examiner also cites Schirbel for the premise that ¹¹C is a PET radioindicator that offers the possibility of authentic labeling of molecules for noninvasive and quantitative determination of physiological functions. The Examiner then states that it would have been obvious to one skilled in the art to combine the teachings of Pagé, Li, and Schirbel to arrive at the present invention.

First, Applicants respectfully submit that a person skilled in the art would have no reason to combine the references. Pagé and Li deal with fundamentally different types of paclitaxel derivatives, both of which are structurally and chemically distinct from each other and from paclitaxel itself. Thus, there is no motivation to combine these references to prepare a non-derivatized and radio labeled paclitaxel as described and claimed in the present application.

Moreover, even if one were to combine the references, one would at best arrive at some water soluble paclitaxel derivative. Both references specifically teach compounds that are derivatives of paclitaxel that are modified to contain a radiolabel, not paclitaxel that is structurally unchanged. The derivatives prepared by Pagé and Li change the properties of the drug being administered, as admitted by each of the references and the Examiner, and then try to draw some conclusions about the non-derivatized drug. It is precisely the inability to make this

connection that the present invention seeks to overcome, i.e. the present invention avoids the need to extrapolate properties of the derivatives to the drug itself, an extrapolation which has been repeatedly found to be invalid. (See, for example, the present specification at page 12, line 7 through page 13, line 21.)

The present invention is not directed towards paclitaxel derivatives, but rather towards paclitaxel in which one of the normally occurring atoms is replaced by a radioactive isotope suitable for PET imaging. Because none of the references teaches the use of non-derivatized paclitaxel, even if one were to combine the references there is no reasonable expectation of success if radio-labeled paclitaxel itself were employed. In particular, each reference is directed toward derivatizing paclitaxel to change its physical properties, i.e. to make it more water soluble. None of the references are concerned with the study of paclitaxel itself, but only with these more water soluble paclitaxel derivatives. Thus, there is no reason to believe that the disclosures of Pagé and Li would be applicable or successful with the less water soluble paclitaxel.

Finally, none of the references, even if combined, teach a person skilled in the art how to make and use the present invention. In all of the references, the only way in which labeling paclitaxel is taught is to label some other compound that is then linked or associated with paclitaxel. None of the references describe a way, nor has the Examiner provided a way, of synthesizing paclitaxel radiolabeled by replacing a naturally occurring atom with a radiolabeled isotope of that atom. Without such an enabling disclosure, the present invention can not be considered obvious.

Applicants thus submit that the presently claimed invention is not obvious in view of the cited references. In particular, (a) there is no motivation to combine the references; (b) even if

one were to combine the references, one would not arrive at the present invention; (c) based on the disclosure of the references, there would be little likelihood of success if it were at all possible to arrive at the invention; and (d) the disclosures of the references do not enable the present invention. Accordingly, Applicants request that the rejection of claims 1-24 as obvious over Pagé in view of Li and Schirbel be withdrawn.

Claims 20-27 and 30-31

With respect to these compounds and method of making claims, Applicants submit that the Examiner has not put forth any rejection that applies to these claims. Claim 20-31 are directed toward a specific genus of chemical compounds. As set forth above, the compounds disclosed in the references of record are structurally distinct from the claimed genus of compounds. The Examiner has set forth no reasonable explanation of how the claimed genus is rendered obvious by the references of record. Accordingly, Applicants submit that these claims are allowable and request that the Examiner indicate their allowability in any subsequent Office Action. If the Examiner does not indicate allowability of these claims, Applicants respectfully submit that the next Office Action cannot be made final. Clarification is respectfully requested.

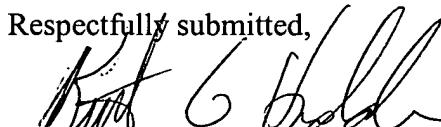
CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. Accordingly, Applicants request that the Examiner indicate the allowability of claims 1-31 and 41-49 and the application

pass to issue. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,


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